Wydase®
(hyaluronidase)

Description
Wydase, a protein enzyme, is a preparation of highly purified bovine testicular hyaluronidase. The exact chemical structure of this enzyme is unknown. Wydase is available in two dosage forms:

WYDASE LYOPHILIZED
Hyaluronidase, dehydrated in the frozen state under high vacuum, with lactose and thimerosal (mercury derivative), is supplied as a sterile, white, odorless, amorphous solid and is to be reconstituted with Sodium Chloride Injection, USP, before use, usually in the proportion of one mL per 150 USP units of hyaluronidase (Wydase Lyophilized).

Each vial of 1,500 USP units contains 1.0 mg thimerosal (mercury derivative), added as a preservative, and 13.3 mg lactose. Each vial of 150 USP units contains 0.075 mg thimerosal (mercury derivative), added as a preservative, and 2.66 mg lactose.

WYDASE STABILIZED SOLUTION
A hyaluronidase injection solution ready for use, colorless and odorless, containing 150 USP units of hyaluronidase per mL with 8.5 mg sodium chloride, 1 mg edetate disodium, 0.4 mg calcium chloride, monobasic sodium phosphate buffer, and not more than 0.1 mg thimerosal (mercury derivative).

The USP and the NF hyaluronidase units are the equivalent to the turbidity-reducing (TR) unit and to the International Unit.

Clinical Pharmacology
Hyaluronidase is a spreading or diffusing substance which modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid, a polysaccharide found in the intercellular ground substance of connective tissue, and of certain specialized tissues, such as the umbilical cord and vitreous humor. Hyaluronic acid is also present in the capsules of type A and C hemolytic streptococci. Hyaluronidase hydrolyzes hyaluronic acid by splitting the glucosaminidic bond between C_1 of the glucosamine moiety and C_4 of glucuronic acid. This temporarily decreases the viscosity of the cellular cement and promotes diffusion of injected fluids or of localized transudates or exudates, thus facilitating their absorption.

When no spreading factor is present, material injected subcutaneously spreads very slowly, but hyaluronidase causes rapid spreading, provided local interstitial pressure is adequate to furnish the necessary mechanical impulse. Such an impulse is normally initiated by injected solutions. The rate of diffusion is proportionate to the amount of enzyme, and the extent is proportionate to the volume of solution.

Animal studies indicated that in dogs, given 160,000 U/kg hyaluronidase intravenously, peak protein excretion in the urine occurred in the first hour and accounted for most of the 82 mg of protein recovered from the urine. The recovery represents 5% of the total amount of protein injected. One hour after the intravenous administration of 160,000 U/kg of hyaluronidase to rabbits, the agent could no longer be detected in the blood (mucin clot assay). It was also noted that the sojourn of hyaluronidase in the blood, as measured by the spreading technique, is considerably longer than the sojourn determined by the mucin clot assay. Rabbits and dogs were given 80,000 to 160,000 U/kg hyaluronidase intravenously, plasma and urine samples were collected and were injected into the shaven skin of another rabbit. The spreading activity (trypan blue as indicator) of the plasma reached a maximum within 5 minutes, remained constant for the first hour, and then declined slowly over 5 hours. The spreading activity of the urine reached a maximum within the first hour and paralleled that of the plasma thereafter.

A study in rats, sacrificed 3 hours after 2,400-3,000 U of radiolabeled hyaluronidase was administered intraperitoneally, indicated that all organs and tissues investigated displayed radioactivity, and that particularly high radioactivity was observed in the thymus, pancreas, kidneys, and ovaries.

Knowledge of the mechanisms involved in the disappearance of injected hyaluronidase is limited. It is known, however, that the blood of a number of mammalian species brings about the inactivation of hyaluronidase. Studies have demonstrated that hyaluronidase is antigenic; repeated injections of relatively large amounts of this enzyme may result in the formation of neutralizing antibodies. The reconstitution of the dermal barrier removed by intradermal injection of hyaluronidase (20, 2, 0.2, 0.02, and 0.002 U/mL) to adult humans indicated that at 24 hours the restoration of the barrier is incomplete and inversely related to the dosage of enzyme; at 48 hours the barrier is completely restored in all treated areas.

Results from an experimental study, in humans, on the influence of hyaluronidase in bone repair support the conclusion that this enzyme alone, in the usual clinical dosage, does not deter bone healing.

Indications and Usage
Wydase is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

Contraindications
Hypersensitivity to hyaluronidase. A preliminary test for sensitivity should be conducted. (See **"Precautions**—LABORATORY TESTS.")

Because of the danger of spreading a localized infection, Wydase should not be injected into or around an infected or acutely inflamed area. Similarly, Wydase should not be injected into an area that is known or suspected to be cancerous.

Warnings
Hyaluronidase should not be used to treat infiltrations of dopamine or alpha agonist drugs.

Precautions
GENERAL
When considering the administration of any other drug with hyaluronidase, it is recommended that appropriate references first be consulted to determine the usual precautions for the use of the other drug; e.g., when epinephrine is injected along with hyaluronidase, the precautions for the use of epinephrine in cardiovascular disease, thyroid disease, diabetes, digital nerve block, ischemia of the fingers and toes, etc., should be observed.

LABORATORY TESTS
A preliminary skin test for sensitivity to hyaluronidase should be performed with an intradermal injection of approximately 0.02 mL of the solution. A positive reaction consists of a wheal with pseudopods appearing within five minutes and persisting for 20 to 30 minutes and accompanied by localized itching. Transient vasodilation at the site of the test, i.e., erythema, is not a positive reaction.

DRUG INTERACTIONS
When hyaluronidase is added to a local anesthetic agent, it hastens the onset of analgesia and tends to reduce the swelling caused by local infiltration, but the wider spread of the local anesthetic solution increases its absorption; this shortens its duration of action and tends to increase the incidence of systemic reaction.

Patients receiving large doses of salicylates, cortisone, ACTH, estrogens, or antihistamines may require larger amounts of hyaluronidase for equivalent dispersing effect, since these drugs apparently render tissues partly resistant to the action of hyaluronidase.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase. It has been observed that intravenous administration of as much as 75,000 U (500 times the therapeutic dose) of hyaluronidase in animals caused no changes in the tissues.

Long-term animal studies have not been performed to assess whether hyaluronidase impaired fertility; however, it has been reported that testicular degeneration may occur with the production of organ-specific antibodies against this enzyme following repeated injections. Human studies on the effect of intravaginal hyaluronidase in sterility due to oligospermia indicated that Wydase may have aided conception. Thus, it appears that hyaluronidase may not adversely affect fertility in females.

PREGNANCY

Teratogenic Effects—Pregnancy Category C

Animal reproductive studies have not been conducted with Wydase. It is also not known whether hyaluronidase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Wydase should be given to a pregnant woman only if clearly needed.

LABOR AND DELIVERY

Administration of hyaluronidase during labor was reported to cause no complications: no increase in blood loss or differences in cervical trauma were observed. It is not known whether Wydase has an effect on the fetus if used during labor; the effect of hyaluronidase on the later growth, development, and functional maturation of the infant is unknown.

NURSING MOTHERS

It is not known whether hyaluronidase is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Wydase is administered to a nursing woman.

PEDIATRIC USE

Hyaluronidase may be added to small volumes of solution (up to 200 mL), such as a small clysis for infants or solutions of drugs for subcutaneous injection. The potential for chemical or physical incompatibilities should be kept in mind. (See **"Dosage and Administration."**)

During hypodermoclysis, special care must be taken in pediatric patients to avoid overhydration by controlling the rate and total volume of the clysis. (See **"Dosage and Administration**, HYPODERMOCLYSIS.")

As in adults, a preliminary test for sensitivity should be conducted prior to the use of this product in pediatric patients. Also, hyaluronidase should not be injected into acutely inflamed or cancerous areas or to enhance absorption of vasoconstricting agents. (See **"Contraindications"** and **"Warnings"**.)

Adverse Reactions

Allergic reactions (urticaria, angioedema) are rare. Anaphylactic-like reactions following retrobulbar block or intravenous injections have occurred. Cardiac fibrillation has been encountered once.

Overdosage

Symptoms of toxicity consist of local edema or urticaria, erythema, chills, nausea, vomiting, dizziness, tachycardia, and hypotension. The enzyme should be discontinued and supportive measures initiated immediately. Agents such as epinephrine, corticosteroids, and antihistamines should always be available for emergency treatment.

Dosage and Administration

Wydase (hyaluronidase) should be administered only as discussed below, since its effects relative to absorption and dispersion of other drugs are not produced when it is administered intravenously.

RECONSTITUTION

If the lyophilized powder for injection is used, 1 mL of 0.9% sodium chloride should be added to a vial containing 150 U of hyaluronidase, and 10 mL of 0.9% sodium chloride to a vial containing 1,500 U of hyaluronidase, respectively, to provide a solution containing approximately 150 U/mL.

ABSORPTION AND DISPERSION OF INJECTED DRUGS

Absorption and dispersion of other injected drugs may be enhanced by adding 150 U hyaluronidase to the injection solution. In order to prepare a solution containing epinephrine, add 0.5 mL epinephrine [Wyeth-Ayerst Epinephrine Hydrochloride Injection, USP (1:1000)] to the above solution.

Before adding Wydase to a solution containing another drug, it is recommended that appropriate references be consulted regarding physical or chemical incompatibilities.

HYPODERMOCLYSIS

Insert needle with aseptic precautions. With tip lying free and movable between skin and muscle, begin clysis; fluid should start in readily without pain or lump. Then inject Solution Wydase into rubber tubing close to needle.

An alternate method is to inject Wydase under skin prior to clysis. 150 U will facilitate absorption of 1,000 mL or more of solution. As with all parenteral fluid therapy, observe effect closely, with same precautions for restoring fluid and electrolyte balance as in intravenous injections. The dose, the rate of injection, and the type of solution (saline, glucose, Ringer's, etc.) must be adjusted carefully to the individual patient. When solutions devoid of inorganic electrolytes are given by hypodermoclysis, hypovolemia may occur. This may be prevented by using solutions containing adequate amounts of inorganic electrolytes and/or controlling the volume and speed of administration.

Hyaluronidase may be added to small volumes of solution (up to 200 mL), such as small clysis for infants or solutions of drugs for subcutaneous injection. *For infants and children less than 3 years old, the volume of a single clysis should be limited to 200 mL; and in premature infants or during the neonatal period, the daily dosage should not exceed 25 mL/kg of body weight; the rate of administration should not be greater than 2 mL per minute. For older patients, the rate and volume of administration should not exceed those employed for intravenous infusion.*

SUBCUTANEOUS UROGRAPHY

The subcutaneous route of administration of urographic contrast media is indicated when intravenous administration cannot be successfully accomplished, particularly in infants and small children. With the patient prone, 75 U of Wydase (hyaluronidase) is injected subcutaneously over each scapula, followed by injection of the contrast medium at the same sites.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

How Supplied

Wydase® Lyophilized is supplied as follows:

150 USP (TR) units of hyaluronidase
NDC 0008-0121-01, 1 mL vial, as single vials.

Not Recommended for IV Use.

Store at controlled room temperature in a dry place. Store sterile reconstituted solution below 30° C (86° F). Use within 24 hours. Following reconstitution, store vial in upright position.

1,500 USP (TR) units of hyaluronidase
NDC 0008-0149-01, 10 mL vial, as single vials.

Not Recommended for IV Use.

Store at controlled room temperature in a dry place. Store sterile reconstituted solution below 30° C (86° F). Use within 14 days. Following reconstitution, store vial in upright position.

Wydase® Stabilized Solution is supplied as follows:

150 USP (TR) units of hyaluronidase per mL
NDC 0008-0170-01, 1 mL vial, as single vials.
NDC 0008-0170-02, 10 mL vial, as single vials.

Not Recommended for IV Use.

Store in a refrigerator.

Do not use if solution is discolored or contains a precipitate.

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